

REMARKS/ARGUMENTS

Claims 13, 14, 23, and 25-34 are pending in the instant application. Claim 33 stands rejected under 35 U.S.C. §112, first paragraph. Claims 13, 14, 23, 25-29, 33 and 34 stand rejected under 35 U.S.C. §103(a) as being unpatentable over United States Patent No. 5,360,840 to Unger in view of either one of United States Patent No. 5,250,285 to Lauffer, United States Patent No. 5,886,173 to Hemmi, or United States Patent No. 5,344,639 to Chiu. Claims 30-32 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Unger in view of either Lauffer or Hemmi or Chiu in further view of United States Patent No. 5,190,744 to Rocklage. The application has been amended. The claims have been amended. Particularly, Claims 33 and 34 have been cancelled, without prejudice to their forming the basis for a continuing application. None of the amendments contravene the proscriptions against new matter prescribed by 35 U.S.C. §132. Reconsideration is respectfully requested.

Claim 33 has been rejected under 35 U.S.C. §112, first paragraph. This rejection has been obviated by the cancellation of Claim 33, without prejudice.

Claims 13, 14, 23, 25-29, 33 and 34 stand rejected under 35 U.S.C. §103(a) as being unpatentable over United States Patent No. 5,360,840 to Unger in view of either one of United States Patent No. 5,250,285 to Lauffer, United States Patent No. 5,886,173 to Hemmi, or United States Patent No. 5,344,639 to Chiu. This rejection is respectfully traversed.

To summarize the following arguments, a combination of Unger and Lauffer is improper as Lauffer teaches away from the claimed combination and it is well settled that references may not be combined when the combination contradicts the teachings of one of those references. Both Hemmi and Chiu teach the use of Eu(II) with their own particular and distinct chelates, not with MRI contrast agents in general as suggested by the Examiner, and provide no motivation for selecting one of their disclosed metal ions for use with chelate of

Unger. Additionally, none of these references provides any motivation for selecting the one of the 82 metal ions from Himmi or the 10 metal ions of Chiu with only certain of the chelates from Unger.

The present invention claims an MRI contrast agent comprising a chelate complex including Eu(II) and a chelate selected from the group of DPTA, EDTA, DTPA-BMA, DO3A, DOTA, HP-DO3, TMT, and DPDP.

Unger discloses a method of imaging diseased vasculature using an MRI contrast agent comprising a paramagnetic metal and a chelating agent. Unger specifically states 10 chelates which are preferred chelates (col. 6, line 41 to 53). Unger also discloses the use of kryptands, a term which does not mean a specific chelate but rather a whole class of chelates. Apart from chelates, Unger also specifically discloses 7 other types of complexing agents (of the same "ranking") like proteinaceous macromolecules (col. 6, line 56 to 60). Moreover, Unger fails to disclose, teach or suggest using Eu(II) as the metal.

Lauffer discloses a contrast agent comprising Eu(II) with a hydroxy-aryl substituted chelate group. These chelates are lipophilic and Eu(II) is suggested as one of 82 possible metal ions which may be suitable for use with those chelates.

With respect to the combination of Unger and Lauffer, the Examiner correctly states that Unger fails to disclose Eu(II) compounds used in a method of imaging regions of decreased vascular perfusion. Further, the Examiner is correct that Lauffer discloses Eu(II). However, the chelates Lauffer discloses are hydroxy-aryl substituted chelates. The hydroxy-aryl groups increase the lipophilicity and hydrophobicity of the chelates and thus of an imaging agent consisting of a metal ion and those chelates. Lauffer teaches that the hydroxy-aryl groups are necessary for his compounds to work as blood pool imaging agents (col. 1, l. 31-64). To the contrary, none of the chelates mentioned in independent claim 23 comprise hydroxy-aryl groups. As the hydroxy-aryl groups are necessary for Lauffer, Applicants respectfully submit that it is therefore improper, lacking motivation, for selecting only the

Eu(II) ion independent of the hydroxy-aryl groups from Lauffer for use with the chelates of Unger.

Furthermore, Applicants submit that Lauffer teaches away from using Eu(II) with a of the present invention for NMR imaging of regions with decreased vascular perfusion, i.e. for blood pool imaging. This becomes clearly apparent from Lauffer's following statement in column 13, line 42-47:

"In contrast, **the ligand DOTA**, which is a known chelate, lacks hydrophobic substituents and as such is unsuitable for NMR image enhancement of the liver and the blood pool".

Clearly Lauffer specifically teaches away from present claim 23, which claims Eu(II)-DOTA-complexes for use in the claimed method. The chelates of the present invention are hydrophilic and not – as the Lauffer chelates – lipophilic. It is well settled that to do what the reference teaches against is the antithesis of obviousness. *In re* Beuhler.

As Lauffer clearly teaches away from combining the references as suggested by the Examiner, Applicant respectfully submits that such combination is improper for being contrary to the teachings of Lauffer. Therefore, the present invention is patentably distinct over Unger and Lauffer. Reconsideration and withdrawal of the rejection are respectfully requested.

With respect to the combination of Unger with Hemmi, Applicant submits that the Examiner has not established a prima facie case of obviousness as neither of the two references contain some motivation for the skilled artisan to modify and then combine the references in accordance with the present invention.

Hemmi discloses MRI contrast agents comprising porphyrin chelates and metal ions.

Contrary to the Examiner's assertion, Hemmi does not generally show the use of Eu(II) in MRI contrast agents. Hemmi only discloses the use of Eu(II) with porphyrins. Hemmi states in column 6 (cited by the Examiner):

The metals represented by M [in Formula II] include both paramagnetic and diamagnetic metals, the former being particularly useful for complexes used as MRI contrast agents, and the latter being particularly useful in photodynamic therapy. brackets added.

Applicants submit that this passage from Hemmi is not describing Eu(II) as being generally applicable for MRI contrast agents, but only as being applicable for use with porphyrin chelates. This passage is describing Formula II of Hemmi's invention, not all MRI contrast agents.

Therefore, Hemmi only stands for the proposition of using Eu(II) with porphyrin chelates, not with the chelates claimed by the present invention. Moreover, neither Unger nor Hemmi provide any motivation for selectively separating one of the metal ions from the complex of Hemmi for combination with one of the chelates of Unger. Eu(II) is suggested by Hemmi as one possible metal ion amongst a total of 82 (41 different metal atoms with oxidation states 2 and 3). Hemmi does not indicate that Eu(II) is more preferred than any of the other mentioned metal ions. Applicants respectfully submit that the Examiner is suggesting it would be "obvious to try" one of these 82 approaches in contravention of *In re* Goodwin (obvious to try is not the standard) and does not establish prima facie obviousness.

Additionally, Hemmi is completely silent about a method of detecting regions with decreased vascular perfusion. The document focuses on a method of synthesizing certain MRI contrast agents. Hence none of the two documents contain some motivation for the skilled artisan to either combine them or to modify the teaching of Unger by using Eu(II) metal ions disclosed by Hemmi.

Even assuming, *arguendo*, that Hemmi and Unger may be properly combined, Applicants respectfully submit that the 10 chelates, 7 complexing agents, and kryptand-class of chelates disclosed by Unger, and the 82 metallic ions of Hemmi may be combined to form over 5740 combinations of complexes, not even counting the myriad combinations available with the whole class of kryptands. Let us conservatively assume that there are only 10 chelates within the class of kryptands. Assuming that is the case, a combination of Unger and Hemmi would result in over 57,000 combinations of complexes. Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case for how one of ordinary skill in the art would have been motivated by these references so as to select the 8 claimed combinations from the over 57,000 combinations suggested by these two references. Applicants submit that such a selection is only arrived at through impermissible reference to the instant application itself.

As neither Hemmi nor Unger provide a motivation for selectively separating and combining their components in a manner claimed by the present invention, Applicants submit that the present invention is patentably distinguishable thereover. Reconsideration and withdrawal of the rejection are respectfully requested.

With respect to the combination of Unger with Chiu, Applicant submits that the Examiner has not established a *prima facie* case of obviousness as neither of the two references contain some motivation for the skilled artisan to modify and then combine the references in accordance with the present invention.

Chiu discloses MRI contrast agents comprising chelates comprising peptide structures. These chelates are not mentioned in our claim 23. Chiu discloses Eu(II) as one of 10 preferred metal ions for use in the disclosed MRI contrast agents, not in MRI contrast agents generally, as stated by the Examiner. In column 3 (cited by the Examiner), Chiu states that:

The contrast agents of the invention are particularly effective when the paramagnetic metal is selected from among divalent or trivalent ions of transition metals or paramagnetic lanthanides. Empasis added.

Again, Applicant submits that this passage does not tout the general applicability of metals such as Eu(II), but only the specific applicability for combining with the disclosed peptides.

Additionally, Eu(II) is not indicated as being more preferred than any other of the 10 mentioned metal ions. Applicants again respectfully submit that the Examiner is suggesting it would be "obvious to try" one of these 10 approaches in contravention of *In re* Goodwin (obvious to try is not the standard) and does not establish prima facie obviousness.

Chiu is also silent about a method of detecting regions with decreased vascular perfusion as we claim it in claim 23. The patent focuses on the complexes, their synthesis and their general use as MRI contrast agents. Hence none of the two documents contain some motivation for the skilled artisan to either combine them or to modify the teaching of Unger by using Eu(II) metal ions as disclosed by Chiu.

Even assuming, arguendo, that Chiu and Unger may be properly combined, Applicants respectfully submit that the 10 chelates, 7 complexing agents, and kryptand-class of chelates disclosed by Unger, and the 10 metallic ions of Hemmi may be combined to form over 700 combinations of complexes, not even counting the myriad combinations available with the whole class of kryptands. Again conservatively assuming that there are only 10 chelates within the class of kryptands a combination of Unger and Chiu would result in over 7,000 combinations of complexes. Applicants respectfully submit that the Examiner has failed to establish a *prima facie* case for how one of ordinary skill in the art would have been motivated by these references so as to select the 8 claimed combinations from the over 7,000 combinations suggested by these two references. Applicants submit that such a selection is only arrived at through impermissible reference to the instant application itself.

Appl. No. 09/830,147
Amdt. Dated November 4, 2003
Reply to Office action of August 4, 2003

As neither Chiu nor Unger provide a motivation for selectively separating and combining their components in a manner claimed by the present invention, Applicants submit that the present invention is patentably distinguishable thereover. Reconsideration and withdrawal of the rejection are respectfully requested.

The rejection of claim 34 has been obviated by its being withdrawn from consideration in the present application. Reconsideration is respectfully requested.

Claims 30-32 stand rejected under 35 U.S.C. §103(a) as being unpatentable over Unger in view of either Lauffer or Hemmi or Chiu in further view of United States Patent No. 5,190,744 to Rocklage. This rejection is respectfully traversed.

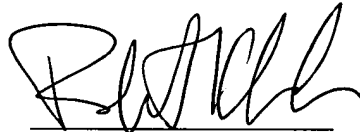
Applicant respectfully submits that as the patentability of the base claims, from which claims 30-32 depend, has been established, the patentability of their dependent claims is also established. *In re* Fine.

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In view of the amendments and remarks hereinabove, Applicant respectfully submits that the present application, including claims 13, 14, 23, and 25-32, is in condition for allowance. Favorable action thereon is respectfully requested.

Should the Examiner have any questions with the foregoing, he is invited to contact Applicant's undersigned counsel at the telephone number listed below.

Respectfully submitted,

A handwritten signature in black ink, appearing to read 'R. Chisholm', written over a horizontal line.

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